MP52. With the indication of the specific sequences in the above amendments, Applicants respectfully submit that this rejection is overcome.

The Office Action apparently asserts that a protein would be claimed which differs from SEQ ID NO:1. Further, the Office Action seems to assume that an arbitrary dimer of a different protein of the TGF-β superfamily would also be claimed. This is incorrect. According to valid claim 28, proteins are comprised which correspond to the fragments of SEQ ID NO:1, but which exhibit little deviations due to their origin from different vertebrates. Moreover, homodimers are claimed, which Applicants believe is unquestionable, since the proteins of the TGF-β family are generally present as homodimers, which could be clearly gathered from the prior art before the filing date.

Further claimed is a combination of these homodimers with another protein of the TGF-β superfamily; it was not intended that a different dimer from the TGF-β superfamily is present alone, although it is possible that the Office Action interprets the claim in such a way.

However, in order to expedite prosecution of this application and even more clearly define the presently claimed invention and to address the above-discussed issues, Applicants have amended claim 28.

The first paragraph on page 4 of the Office Action objects again that fragments, parts and heterodimers of the members of the TGF-β superfamily are not be sufficiently disclosed. Although Applicants disagree with the Office Action on this issue, such fragments, parts or heterodimers are no longer contained in the present claims, hence the objections in this passage are believed to be overcome. Applicants further point out that the Office Action is not correct in assuming that it was not known which specific domains

and sequences of the members of the TGF-β superfamily exhibit corresponding features. A variety of references and patent applications or publications, respectively, particularly show the sequences of the members of the TGF-β superfamily, which are responsible for cartilage and bone growth. A lack of guidance can by no means be acknowledged in this case and the fragments, parts and heterodimers objected by the Examiner are not longer subject matter of the presently claimed invention in any case.

As discussed above, the newly submitted claims only comprise MP52 proteins and particularly mentioned fragments thereof, respectively.

For at least the above reasons, Applicants respectfully submit that claims 17-29 fully comply with 35 USC §112, first paragraph. Applicants respectfully request that these rejections be reconsidered and withdrawn.

The Office Action rejects claims 17-29 under 35 USC §103(a) as being obvious over Urist et al. (U.S. Patent No. 4,596,574) in view of Oppermann et al. (WO 91/05802), Yan et al. (1995), Fujino et al. and Hoetten et al. This rejection is traversed as it may apply to the amended claims.

In the January 17, 2001 Office Action, no rejection was made under 35 USC §103(a) of claim 16. In good faith, Applicants incorporated the subject matter of claim 16 into the independent claims. Now, in the September 7, 2001 Office Action, the Examiner asserts that Applicants' Amendment necessitated the new grounds of rejection. It is unclear to Applicants how incorporating the subject matter of a claim (16) that is not rejected to that of a rejected claim necessitates a new ground of rejection since such a rejection clearly could have been made earlier against claim

16. Thus, it is respectfully submitted that Applicants' amendments did not necessitate the new grounds of rejection and the deeming of the Office Action as "Final" is improper. Clarification of this issue is respectfully requested. Also, reconsideration and withdrawal of the improper "finality" of the Office Action are respectfully requested.

In any case, amended claim 28 is no longer directed to "a bioactive matrix material", but to crystallographically phase-pure materials, i.e. mixed phases as were applied in the state of the art are excluded. The term "crystallographically phase-pure material" is mentioned in paragraph 1 on page 1 of the present specification and is also explained in more detail throughout the specification. For example on page 6, starting with the last paragraph, the disadvantages of the prior art are referred to and the fact that these disadvantages can be avoided by using crystallographically phase-pure implant materials. Also on page 13, first paragraph, there are explanations on the crystallographically phase-pure α- or β-tricalcium phosphate ceramics used according to the invention.

It is already stated in the description that materials according to the state of the art consisted of mixtures from different calcium phosphates. In the production of the materials according to the invention, however, e.g. tetracalcium phosphate and dicalcium phosphate are avoided (cf. page 16, second paragraph). The crystallographic purity is an essential precondition for the positive characteristics of the matrix of the present application. The phase purity in combination with the defined microporous structure guarantees a predictable resorption and thus also a controlled release, as already stated at the bottom of page 14. It also contributes to avoid connective tissue infiltration and activation of

macrophages, as indicated at the top of page 7 (all citations referring to the specification of the present application).

Urist certainly did not use a phase-pure matrix and detected correspondingly negative side effects. Phase purity is not mentioned in the article Yan et al., but, rather, that a low-melting point adhesive agent (from something like low melting phosphate glass) is added to β-TCP. Nowhere in this article can it be found that this matrix is applied with BMPs. For the Examiner's courtesy, Applicants have prepared and enclose a translation of the Yan et al. article. As can be gathered therefrom (cf. item 2.1 composition), the materials were produced by mixing a tricalcium phosphate powder with a suitable binding material. In the test described phosphate glass having a low melting point is used as binding material. From this article, it can also be gathered that, although the main part of the material corresponds crystallographically to β-TCP, there are apparently also further materials present, namely, among other things, this binding material.

Within the frame of the present invention it was desirable to employ absolutely phase-pure material. Therefore the material described by Yan et al. is unsuitable due to undesired additives.

The article by Yan et al. does therefore not exceed the disclosure of Urist, and, further, is not related to growth factors.

Applicants also respectfully submit that the newly applied US 5,866,155, and in particular in the parts cited thereof (column 3, line 14 to column 4, line 32), only polyester copolymers are described, and not calcium phosphates such as TCP. Furthermore, the described methods are thus only to be applied to these artificial polymers (PLAGA). This reference rather supports the view that phase purity is something special, since it is stated

in the passage bridging columns 1 and 2: "Most calcium phosphate biomaterials are polycrystalline ceramics...".

For at least the above reasons, the presently claimed invention would not have been obvious over any combination of the applied references and reconsideration and withdrawal of the rejection of claims 17-29 under 35 U.S.C. § 103(a) are respectfully requested.

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not being timely filed, Applicants respectfully petition for an appropriate extension of time. Any fees for such an extension together with any additional fees may be charged to Counsel's Deposit Account 01-2300.

Respectfully submitted,

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AMENDED CLAIMS MARKED UP TO SHOW CHANGES

Amend claims 17, 20, 21, 23, 26 and 28 as follows:

17. (Twice Amended) The implant material of claim 28, wherein the [bioactive] matrix material is composed of a tricalcium phosphate ceramic comprising crystallographically phase-pure α- or β-tricalcium phosphate ceramic with an interconnecting microporosity of 20-60% of its volume.

20. (Amended) The implant material of claim 17, wherein the calcium phosphate matrix [first component] degrades over time to release the MP52 protein or DNA encoding such MP52 protein [second component] in a controlled retarded manner.

21. (Twice Amended) A process for the production of an implant material according to claim 28, the process comprising applying the MP52 protein or DNA encoding such MP52 protein [second component] in and/or on the calcium phosphate matrix [first component] as a solution in a solvent such that a homogeneous distribution of the MP52 protein or DNA encoding such MP52 protein [second component] in and/or on the calcium phosphate matrix [first component] is achieved.

23. (Amended) The process of claim 21, wherein the MP52 protein or DNA encoding such MP52 protein [second component] is concentrated by *in situ* precipitation from the solvent in the calcium phosphate matrix [first component] by admixing a precipitating solvent.

26. (Amended) A method of use selected from the group consisting of a treatment of a bone defect, a sinus lift, a cyst filling in the jaw region, a bone fracture, a bone replacement, an application in cosmetic, [and] plastic surgery and in the dental region, and immobilizing movable bone parts in a patient in need thereof, the method comprising implanting an implant material according to claim 28 into the patient.

28. An implant material suitable for cartilage and/or bone growth comprising a [bioactive] matrix material which is composed of a crystallographically phase-pure calcium phosphate and applied in and/or on said [this bioactive] matrix a cartilage inducing and/or bone inducing MP52 protein or a DNA encoding such MP52 protein, wherein the MP52 protein is selected from the group consisting of

(a) a protein comprising amino acid 1 to 501, 28 to 501, 361-400 to 501, 381 to 501, 382 to 501, 400 to 500 of SEQ. ID. No. 1,

(b) [a protein sequence according to (a) which differs from SEQ. ID. No. 1 due to the origin of the protein from other vertebrates but has essentially the same cartilage and/or bone including activity as (a),

(c)] a protein according to (a) [or (b)] which is a homodimer, and

(c) [(d)] a protein according to (b) [(c) and] in combination with a dimer of another protein of the TGF-β superfamily [, and

a protein using the same receptor mechanism as a protein according to (c)].